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10/089,501	04/22/2002	Hiroyuki Saito	053466-0325	9449

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EXAMINER	
BURKHART, MICHAEL D	
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1633	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/089,501	SAITO ET AL.	
	Examiner	Art Unit	
	Michael Burkhart	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 January 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *45-49 and 51-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *45-49 and 51-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt and entry of the amendment dated 1/2/2008 is acknowledged. After entry of the amendment, claims 45-49, and 51-56 are pending and under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Claim Objections

Claim 45 is objected to because of the following informalities: "chimera" in line 6 should be "chimeric". Appropriate correction is required.

Claim Rejections - 35 USC § 112

Claim 53 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new rejection necessitated by applicants' amendment of the claims in the response filed 1/2/2008. This is a New Matter rejection.**

Amended claim 45 (from which claim 53 depends) recites a method of administering antibodies "having a human antibody constant region". The specification provides support for this amendment regarding the broad scope of, for example claims 45-49. However, claim 53 recites antibody fragments (e.g. Fab, scFv) that do not comprise a constant region, but rather, are comprised entirely (or primarily) of variable regions. There is no disclosure in the specification

of Fab or scFv fragments that comprise a human constant region. Rather, it is taught (on page 26) that scFvs are obtained by linking variable regions as, for example, taught in Huston et al (PNAS, 1988). A review of Huston et al reveals no constant region in scFvs. Therefore, there appears to be no support for the antibody fragments listed in claim 53 that comprise a constant region. Thus, the amended claim includes impermissible New Matter.

Claims 45-49 and 51-56 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This rejection is maintained for reasons made of record in the Office Actions dated 4/18/2006, 12/27/2006, 7/3/2007, and for reasons set forth below.**

Response to Arguments

Applicant's arguments filed 1/2/2008 have been fully considered but they are not persuasive. Applicants essentially assert that: 1) the specification demonstrates that the growth of blood vessel tissues by TF is suppressed by the i-b2 antibody, which is sufficient to demonstrate to one of skill in the art that applicants were in possession of the claimed invention; 2) the site to which antibody ib-2 binds has been shown to be significant for the action of TF on blood vessel tissue growth, and, as set forth in the MPEP, disclosure of an antigen is considered adequate written description of an antibody claimed by its affinity for the antigen; 3) the instant claims are defined by the structure of the antibody and binding site of the antigen, and antibodies of the

present invention can be easily obtained by the method of reference Example 7; 4) the epitope of the claimed antibody i-b2 is disclosed, as is the CDR of antibody i-b2.

Regarding 1) -3), the specification does not disclose a general inhibition of blood vessel growth by the claimed antibodies, rather, as set forth in the three previous Office Actions, antibody ib-2 prevents narrowing of the blood vessel lumen, suggesting it can prevent restenosis. The specification does not disclose using antibody ib-2, or any other α-TF antibodies, for treating angiogenesis or neovascularization. That is, there is no literal support for these aspects of the claimed invention. Thus, the disclosure must inherently support these aspects of the claimed invention, which it does not for reasons of record. There is nothing in the specification or prior art to indicate applicants considered using the claimed antibodies to treat angiogenesis or neovascularization.

> "It is not sufficient for purposes of the written description requirement of Section 112 that the disclosure, when combined with the knowledge in the art, would lead one to speculate as to modifications that the inventor might have envisioned, but failed to disclose." *Lockwood v. American Airlines Inc.,* 41 USPQ2d 1961, 1966 (CAFC 1997).

Further regarding 2) and 3), the claims are not directed to antibodies, but rather to methods of using antibodies to treat a broad range of disease. Thus, asserting written description of an antibody exists via description of its cognate antigen is not persuasive when the claimed invention are methods of treating disease wherein the antibodies must have a specific function, not merely bind an antigen.

Regarding 4), a review of the specification reveals no epitope mapping for antibody ib-2, and applicants do not point to ant passage which supports this assertion. That the CDR for

antibody ib-2 is disclosed is not in question, however, applicants fail to point out how description of a CDR of a single antibody can provide written description for treatment of diseases that is are disclosed in the specification.

Claims 45-49 and 51-56 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using humanized α-TF antibodies that prevent the activation of Factor X by a complex of TF/Factor VII to suppress restenosis, does not reasonably provide enablement for using such antibodies to suppress any other types of blood vessel growth, e.g. angiogenesis or neovascularization. **This rejection is maintained for reasons made of record in the Office Actions dated 4/18/2006, 12/27/2006, 7/3/2007, and for reasons set forth below. It is noted that the scope of this rejection has been changed due to amendment of the claims to more accurately reflect the activity of the claimed antibodies, i.e. the claims no longer require antibodies that inhibit binding of Factor X to human TF.**

Response to Arguments

Applicant's arguments filed 1/2/2008 have been fully considered but they are not persuasive. Applicants essentially assert that: 1) the specification demonstrates that the growth of blood vessel tissues by TF is suppressed by the claimed antibodies, and because restenosis, angiogenesis, and neovascularization all share in common TF expression, this is sufficient to show enablement of the claims for all of the above diseases; 2) the Zhang et al reference demonstrates that inhibition of TF expression by antisense RNA inhibits VEGF/VPF transcription; 3) the instant claims have been amended to recite humanized antibodies, removing concerns of the HAMA response to non-human antibody sequences; 4) the antibodies b-b and i-b

are very similar to antibody i-b2 in sequence and function (i.e. inhibition of Factor X activation), thus, the claims are enabled for these antibodies as well as for i-b2; 5) from the teachings of Zang et al, the present disclosure confirms that even if the roles of TF in "tumor and coagulation/restenosis" [sic] are different, the site to which the presently claimed antibodies bind inhibits blood vessel growth.

Regarding 1, 2), and 5), the role of TF expression in these diseases is not in dispute, however, there is no demonstration of any antibodies that can inhibit TF expression. Further, as set forth in the previous Office Action, the role of TF in angiogenesis/ neovascularization versus its role in restenosis is quite different. Thus, inhibition of Factor X activity by an antibody in order to prevent restenosis or coagulation does not automatically equate with suppression of its role in the increase of growth regulatory molecules, such as VEGF/VPF.

Further regarding 1), the specification does not disclose a general inhibition of blood vessel growth by the claimed antibodies, rather, as set forth in the three previous Office Actions, antibody ib-2 prevents narrowing of the blood vessel lumen, suggesting it can prevent coagulation-based diseases or restenosis, and no other disease. This is quite different from the requirements of angiogenesis or neovascularization, which require new vessel growth, not merely the narrowing of the lumen of a vessel that is already present, i.e. restenosis. There is nothing in the instant disclosure or the art of record to link the narrowing of the blood vessel lumen with angiogenesis or neovascularization. Further regarding 5), Zhang et al is silent regarding the inhibition of the activity of TF/Factor VII by TF-specific antibodies.

Regarding 3), this does not remove other concerns of antibody therapy for angiogenesis set forth in the previous Office Action, such as limited tissue penetration and physiological barriers to antibody penetration of tumors.

Regarding 4), due to amendment of the claims and the data set forth in Figs 1-4, this aspect of the enablement rejection is withdrawn.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 45-49 and 52 are rejected under 35 U.S.C. 102(e) as being anticipated by Wong et al (U.S. Patent 5,986,065, EFD 3/10/1997). **This is a new rejection necessitated by amendment of the claims to more accurately reflect the activity of the claimed antibodies, i.e. the claims no longer require antibodies that inhibit binding of Factor X to human TF, antibodies not taught in the prior art.**

Wong et al disclose teach TF-specific antibodies that bind human TF and that inhibit the activation of Factor X by the TF/Factor VIIa complex, and can be used for treatment of, for example, restenosis. See the abstract, Figs. 4, 6A, 6B, 7, column 3, lines 18-37, column 5, 19-35. The antibodies may be chimeric, or humanized, by using a human constant region with a non-human variable region (column 8, lines 46-67). The antibodies may be monoclonal or

polyclonal (column 7, lines 46-49). Absent a definition in the specification for "recombinant", "altered", or "modified" antibodies as recited in claims 48, 49, and 52, the production of humanized chimeric antibodies taught by Wong et al is considered to teach these limitations. This is because a reasonably broad interpretation of these terms encompasses the humanized chimeric antibodies of Wong et al, e.g. the native non-human antibodies were "modified" or "altered" to include a human constant region, or a "recombinant".

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Burkhart whose telephone number is (571)272-2915. The examiner can normally be reached on M-F 8AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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/Michael Burkhart/
Primary Examiner, Art Unit 1633